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Negative HIV encephalitis and meningoencephalitis management algorithm Decision-making

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Abstract

Meningoencephalitis is a serious, relatively frequent infection, with a worldwide incidence of 3.5 to 7.4 per 100,000 inhabitants per year and a high mortality rate (10 to 12%). The objective of our work was to determine the etiologies of encephalitis and meningoencephalitis using the most modern microbiological diagnostics and to propose a management algorithm diagnosis.

Materials and methods: This is a prospective descriptive study of 141 patients aged over 28 days with symptoms suggestive of HIV-negative encephalitis and meningoencephalitis during the period from April 1, 2012 to August 31, 2015. Several types of analyzes of the various samples (LCS, serum, nasopharyngeal samples) were carried out, including 2671 by PCR, 404 direct examinations and bacterial culture, 219 viral cultures and 380 serologies. The number of pathogens screened for the patients included in this study varied from 1 to 31 pathogens.

Results: In Batna, a wide range of pathogens cause acute encephalitis. Of the 141 patients, 111 (78.7%) had at least one etiological diagnosis (63 certain, 80 probable and 32 possible). Diagnosis was confirmed for 58 (41.2%) patients, probable for 41 (29.1%), and possible for 12 (8.5%). The overall incidence of encephalitis in our region is 2.15 / 100,000 inhabitants with an average age of 30.8 years (standard deviation = 21.5 years). The most frequently identified etiological pathogen was KB 30 (21.3%), followed by EBV 20 (14.2%), HSV 14 (9.9%), CMV 11 (7.8%), Coronavirus 18 (12.5), and Adenovirus 6 (4.3%).The search for patients with a confirmed and/or probable monomicrobial agent, numbering 53 (37.6%), was essential to come out with a decision-making algorithm regarding the diagnostic approach. Coinfections were identified for 48 patients (34%), of whom 12 (8.5%) had more than 2 pathogens found. 21.3% of cases remained of undetermined cause. Evolution was unfavorable for 67 or 47.2%. There were 43 cases of death (30.5%), with 20 cases of after-effects.

Conclusion: This study made it possible to highlight for the first time the etiologies of encephalitis and meningoencephalitis with their clinical and para-clinical particularities, in the region of eastern Algeria (Batna), which allowed the development of a decision-making algorithm for the diagnostic approach allowing rapid and appropriate care for our patients.

Keywords: HIV negative; Encephalitis; Meningoencephalitis; Batna; Algeria

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1. Introduction

Encephalitis is an inflammatory condition of the brain tissue responsible for neurological dysfunction, sometimes of infectious origin or not, they can evolve in an acute, subacute or chronic mode (1, 2). They are relatively frequent (incidence in the world: 3.5 to 7.4 per 100,000 inhabitants per year) (1), resulting in high mortality (10 to 12%) or sometimes heavy sequelae for the survivors (25.5-46.5 %) (3-6).

Infectious encephalitis is more common in young children, people over 65, and immunocompromised people (7). It is sometimes associated with meningeal involvement (meningoencephalitis) (8) or spinal cord involvement (encephalomyelitis) (9). In these infectious attacks, it is necessary to differentiate the acute attacks comprising cerebral lesions caused by the invasion and the replication or the multiplication of the infectious agent within the cerebral parenchyma from the so-called post-infectious attacks for which the infectious agent is absent in the central nervous system (CNS) (6). During primary acute encephalitis, different anatomical sites can be affected and the topography of the sometimes-necrotic lesions observed points towards an etiological diagnosis. For these attacks, the penetration of the infectious agent into the CNS is done either by crossing the blood-brain barrier, or via retrograde neuronal transport (6). Post-infectious encephalitis reflects an "aberrant" immunological reaction developed against white matter antigens during an infectious syndrome. There is no infectious agent or necrotic lesions in the CNS (8). Despite a better understanding of the pathophysiological mechanisms and technological advances that make it possible to considerably improve the diagnosis of infectious encephalitis, in particular thanks to PCR (10), revealing the major role of HSV, Mycobacterium tuberculosis and listeria monocytogenes, particularly in developing countries, the etiological diagnosis of encephalitis remains difficult and the etiology of infectious encephalitis is undetermined in nearly half of the cases (5, 6). However, it has been shown that an accurate diagnosis allows better therapeutic management and a reduction in mortality and morbidity associated with infectious encephalitis. This better management of patients with infectious encephalitis is a major challenge, particularly developing countries and requires combining the use of the most effective diagnostic means by preferentially targeting the most common pathogens in order to initiate appropriate treatment as soon as possible (10).

The objective of our work was to determine the etiologies of encephalitis and meningoencephalitis using the most modern microbiological diagnostics and to propose a diagnostic management algorithm.

2. Material and methods

This prospective descriptive study was carried out on HIV negative patients, aged 28 days and over, admitted in the infectious diseases department, in pediatrics, or in medical intensive care unit of the Batna University Hospital in Algeria between April 1st, 2012 and August 31st, 2015 and meeting the following case definition: patients aged over 28 days presenting with fever ≥ 38°C and having the following clinical signs: impaired consciousness, convulsions, focal neurological signs or generalized (central or peripheral), neurovegetative disorders, psychiatric disorders and patients for whom a clear CSF was collected on admission.

The exclusion criteria were: HIV-positive patients, patients with a brain abscess and patients with documented non-infectious pathology. Clinical data were collected including demographic elements, interview elements and clinical elements describing the signs and symptoms presented by the patient when included in the study, as well as a severity score (Glasgow score). Clinical follow-up of patients was carried out in order to monitor the progress of the patients. Meanwhile, an EEG was carried out for 61 patients, and Imaging was systematically carried out for 139 patients, except for two patients for whom the diagnosis of cerebral malaria was obvious.

Biological data were collected on a biological information sheet; this biological information sheet collected all the microbiological and non-microbiological data used to classify the cases, during inclusion, and for monitoring the patient's care. Samples were taken on admission according to the standards for the management of suspected cases of encephalitis. In addition, for the purposes of additional microbiological investigations, samples were taken and immediately frozen at -80°C for subsequent analyses: Blood on EDTA tube (5 ml) or on dry tube (5 to 10 ml), Throat swab, CSF (1 tube of 15 drops each). These samples were supplemented with blood in an EDTA tube (5 ml) or in a dry tube (5 ml) taken when the patient left. In our study, lumbar puncture (LP) was performed in 131 (92.9%) patients. This LP is missing for 10 patients (7.1%) because 4 had pupillary edema, 2 had spondylodiscitis and 4 had cerebral malaria. Due to lack of volume, glycorrhachia was only performed on 129 CSF (98.47%) and albuminorachia on only 124 CSF (94.65%). Additional analyzes (PCR, viral culture and serological tests) were carried out secondarily at the Institute of Infectious Agents (IAI) of Lyon University Hospital. The list of pathogens searched for and analyzes carried out are listed in tables No. 1, 2 and 3. Additional molecular analyzes were carried out according to the standards of the

IAI microbiology laboratories. The samples were extracted using Nuclisens Easymag (Bio Mérieux). After carrying out the extractions, the different real-time PCR/RT-PCR were carried out for the detection of viruses and bacteria listed in Table No. 1

Table 1 PCR performed on our samples

PCR	CSF	Serum	Pharyngeal swabs
HSV1, HSV2	+	+	+
VZV	+	+	+
Mycoplasma	+	+	+
Chlamydiae	+	+	+
EBV	+	+	-
CMV	+	+	-
HHV6	+	+	-
Enterovirus	+	+	-
Adenovirus	+	+	-
Listeria	+	+	-
Coxiella	+	-	-
Bartonella	+	-	-
Trophyeryma whipplei.	+	-	-
Influenza A	+	-	+
Influenza B	+	-	+
Coronavirus	-	-	+
Pico virus (amorces entérovirus, rhinovirus)	-	-	+
Parechovirus	+	-	-
BK virus	+	+	-
Measles	+	+	-
Rubella	+	+	-
Mumps	+	+	-

Viral isolation techniques were applied to throat samples stored at -80°C, diluted 1/10 and inoculated into a culture of monkey kidney cells. These culture data supplemented those carried out in the Microbiology Batna ‘s hospital department (table 2).

Table 2 Cultures practiced on our samples

Culture	CSF	Blood	Pharyngeal swabs	Other sites
BK	+	-	-	+
Pyogen agents	+	-	-	-
Viral culture	-	-	+	-
A&B influenza culture	-	-	+	-
1,2,3 flu culture	-	-	+	-

Serological diagnosis was carried out for some pathogens, using the two collected serums , and sometimes the CSF. The list of pathogens screened for by seroconversion is given in table n°3.

Table 3. Performed serologies on our samples

Serologies	CSF	Serum
Mycoplasme	-	+
Chlamydiae	-	+
Bor relia de Lyme	+	+
Coxiella	-	+
Rickettsies Rickettsie	-	+
Rickettsies Typhi	-	+
Rickettsies Conorrii	-	+
West Nile	-	+
Toscana	-	+
Bartonella		+

The etiological investigation was carried out in accordance with the FLIPS recommendations for the treatment of patients with encephalitis (11) whose recommended diagnostic procedure is divided into 3 successive stages depending on the frequency of infectious agents as a cause of the encephalitis and the need to start early treatment for certain pathogens. Depending on the result, the etiology identified for each case is classified as confirmed, probable, possible, or unknown. Each case can be affected by more than 1 etiology. The interpretation of these results can sometimes be difficult; it must always be done according to the clinical context, the isolated virus and knowledge of the patient's immune state (12, 13).

Data was entered and analyzed by the EPI info 7 software. The descriptive statistics were presented in the numbers form and percentages for the qualitative variables, and in averages form with standard deviation, median and range for the quantitative variables. For the comparison of the quantitative variables, we used the Chi-2 test with a risk of error α of 5%.

The rules of ethics, related to medical secrecy and patient consent were respected. We were able to test 2671 PCR samples, 404 direct examinations and bacterial culture, 219 viral cultures and 380 serologies.

3. Results

141 patients met the HIV-negative case definition for encephalitis and meningoencephalitis; The overall incidence was 2.15 / 100,000 inhabitants variable from one year to another with an average age of our 30.8 years (standard deviation = 21.5 years), the incidence observed during our work is 9.58 encephalitis/100,000 hospitalizations. Due to the use of the algorithm, and the performance of on-site analyses, the number of pathogens sought for the patients included in this study varied from 1 to 31 pathogens. For 13 patients, only one diagnostic test was performed because it was immediately positive, while for others, the entire battery of tests had to be performed. On average, the number of tests that have been performed in patients for whom an etiology was identified is lower than in patients for whom no etiology was found (15.01 vs 20.17). Totally, 111/141 had at least one etiological mentioned diagnosis (63 certain, 80 probable and 32 possible). For 48 patients, signs of infection by several pathogens were found, suggesting possible co-infections, or the presence of pathogens not involved in the meningoencephalitis process, of which 12 (8.5%) had more than 2 pathogens found. For 111/141 patients, at least one microbiological examination made it possible to identify an etiological agent. The diagnoses were as follows: certain for 58 patients (with 5 co-infections); 17 (15.3%) of BK, followed successively by EBV 12 (10.8%), Streptococcus pneumonae 7 (6.3%), CMV 5 (4.5%), Adenovirus 4 (3.6%), N. meningitidis 3 (2.7%), Enterovirus 1 (0.9%), HSV 2 cases (1.8%) as well as brucellosis 2 (1.8), 1 case (0.9%) for Lyme, 1 case (0.9%) Mumps, 1 case (0.9 %) Rubella, 1 case (0.9%) Acinetobacter, 1 case (0.9%) Klebssiella.

Diagnosis was probable for 41 patients (with 39 coinfections); Coronavirus 7 (6.3%), followed by 4 cases (i.e. 3.6%) of tuberculosis, 3 cases of malaria (3.6%), 5 cases of HSV (2.7%), 3 cases of VZV (2.7%), 3 cases of CMV (2.7%), 2 cases of

EBV (1.8%), 2 cases of adenovirus (1.8%), 2 cases of Listeria (1.8%), 2 cases of enterovirus (1.8%), 2 cases HHV6 (1.8%), 2 cases of influenza A (1.8%), 1 case of influenza B (0.9%), 1 case of Rubella (0.9%), 1 case of BK virus (0.9%), 1 case (0.9%) of Creutzfeldt Jakob; and possible for 12 patients (with 20 co-infecting pathogens); These were 5 cases of tuberculosis with a frank clinical form, one case of VZV with shingles. At the same time, 3 cases of rickettsioses are suspected based on serological data, 3 cases of *C. Burnetii*. For all documented infections (certain, possible and probable), an etiological agent was detected as a monomicrobial in 63/141 patients, i.e. 44.7% of cases (see Table 4). The 3 most frequent diagnoses were tuberculosis (17 cases or 12.1% of cases), EBV (7 cases or 4.3%) and CMV (5 cases or 3.5%). For 10 of these patients, the diagnosis was only possible (5 TBC, 3 *Coxiella burnetii*, 2 *Rickettsia* (*Typhi, Conorrii)).*

Table 4 Nature and frequency of etiological agents detected in isolation per patient

Etiological diagnosis	**N=6 3**	**%**
KB	17	12.1
EBV	7	5
CMV	5	3.5
N. meningitidis	3	2.1
Coronavirus	4	2.9
Adenovirus	3	2.1
S.Pneumoniae	3	2.1
Coxiella Burnetii	3	2.1
HSV	2	1.4
Rubella	2	1.4
Brucellosis	2	1.4
Plasmodium Falciparum	2	1.4
Enterovirus	1	0.7
Mumps	1	0.7
HHV6	1	0.7
Influenzae A	1	0.7
VZV	1	0.7
Creutzfeld Jacob	1	0.7
R.Typhi	1	0.7
R.Conorri	1	0.7
Klebssiella	1	0.7
Acinetobacter	1	0.7
TOTAL	63	44.7%

* % calculated on 141 patients included

The patients seeking with a confirmed and or probable monomicrobial agent 53 numbered (37.6%) was essential to come out with a decision-making algorithm as to the diagnostic approach. onset was gradual in (52.8%); Meningoencephalitis was more notable for the majority of infectious agents (77.4%); lymphocyte in (54.7%). Polynuclear reaction could be observed during EBV (28.6%), CMV (20%), Coronavirus (25%) infections. Transient hypoglycorachia was evident during EBV infection (57.1%). The coronavirus was probably responsible for meningoencephalitis in 100% cases with a lymphocyte reaction in 50% cases. In addition, it appears that CMV infections are much more frequent in the elderly (>65 years old), and that respiratory disorders associated with meningoencephalitis are observed preferentially with respiratory pathogens (BK, Pneumococcus). Finally, in terms of complementary investigations, the EEG is much less informative than neuroimaging (tables 5 a&b).

Table 5a Demographic and description data of neurological lesions of the 53 cases with confirmed or probable monomicrobial agents

Demographic, Clinic Data	**BK=12**	**EBV=7**	**CMV=5**	**Corona=4**	**Adéno=3**	**Pneumo=3**	**Méningo=3**	**HSV=2**	**Brucelle=2**	**BGN=2**	**Plasmodium=2**	**other virus=7**
Medium age	35(20-73)	34(5-61)	70 (4-70)	29.5 (19-45)	13 (10-21)	21 (1-61)	1 (1-14)	48.5 (48-9)	43 (36-50)	22.5 (11-4)	29.5 (23-36)	21 (2-41)
Male	5 (41.7)	3 (42.9)	3 (60)	4 (100)	3 (100)	2 (66.7)	2 (66.7)	1 (50)	1 (50)	2(100)	2(100)	2 (28.6)
Tobacco	4 (33.3)			1 (25)							1 (50)	1 (14.3)
Sudden start		5(71.4)	3 (60)			3 (100)	3 (100)	1 (50)		1 (50)	2 (100)	5 (71.4)
Ongoing start	12 (100)			3 (75)	2 (66.7)			1 (50)	2 (100)			
Rhinorrhea		1(14.3)	2 (40)	1 (25)	1 (33.3)	2 (66.7)	1 (33.3)					1 (14.3)
Headaches	12 (100)	5 (71.4)	2 (40)	4 (100)	2 (66.7)	2 (66.7)	2 (66.7)	2 (100)	1 (50)	2(100)	2 (100)	5 (71.4)
Neck stiffness	7 (58.3)	6 (85.7)	1 (20)	2 (50)	1 (33.3)	2 (66.7)	3 (100)			2 (100)		3 (42.9)
Agitation	5(41.7)		2 (40)	2 (50)		2(66.7)				1 (50)	1(50)	1(14.3)
Confusion	3 (25)		1 (20)		1(33.3)	1 (33.3)						1 (14.3)
cranial pairs Impairment	8(66.7)	1 (14.3)	3 (60)	2 (50)	3 (100)				2 (100)	2 (100)		4 (57.2)
Glasgow<8	6(50)	1 14.3)	2 (40)	1 (25)	2 (66.7)	1 (33.3)		1 (50)		1 (50)	1 (50)	
Convulsions	7(58.3)	2(28.6)	2 (40)	1 (25)	1 (33.3)	1 (33.3)	1 (33.3)	1 (50)		1 (50)	1 (50)	2 (28.6)
Psychiatric disorders	4(33.3)											
Respiratory impairment	10(83.3)	2 (28.6)	1(20)	1(25)		2 (66.7)	2(66.7)	1(50)				
Rash			2(40)	1(25)			2(66.7)					1(14.3)

Table 5b Biological, radiological and evolving data of the 53 cases with confirmed or probable monomicrobial agents

Biological, radiological and evolutionary data	**BK=12**	**EBV=7**	**CMV=5**	**Corona=4**	**Adéno=3**	**Pneumo=3**	**Méningo=3**	**HSV=2**	**Brucelle=**	**BGN=2**	**Plasmodium =2**	**Autres virus=7**
Cells ≥4e /ml	10 (83.3)	6 (85.7)	2 (40)	4 (100)	2 (66.7)	3 (100)	3 (100)	1 (50)	2 (100)	2 (100)		5 (71.4)
Lymphocytes	6 (50)	3 (42.9)	4 (80)	2 (50)	3 (100)			2 (100)	2 (100)			6 (85.7)
Polynuclear	2 (16.7)	2 (28.6)	1 (20)	1 (25)		3 (100)	3 (100)			2 (100)		1 (14.3)
Variegated	2 (16.7)	1 (14.3)		1 (25)								
Hypoglycorachie	9 (75)	4 (57.1)	1 (20)	1 (25)		3 (100)	3 (100)		1 (50)	2 (100)		
Hypoglycorachia	9 (75)	4 (57.1)	2 (40)	2 (50)	2 (66.7)	1 (33.3)	3 (100)	1 (50)	2 (100)	1 (50)		3 (42.9)
Hyponatremia	9 (75)	3 (42.9)	2 (40)			1 (33.3)	1 (33.3)	1 (50)		1 (50)		2 (28.6)
Pathological neuroimaging	11 (91.7)	6 (85.7)	5 (100)	2 (50)	2 (66.7)	2 (66.7)			2 (100)	1 (50)		2 (28.6)
Abnormal EEG	1 (8.1)	1 (14.3)		2 (50)	1 (33.3)	1(33.3)		1 (50)				2 (28.6)
Intensive care admission	3 (25)	2 (28.6)	2 (40)		2 (66.7)			1 (50)		1 (50)	1 (50)	1 (14.3)
Death	5 (41.7)	3 (42.9)	2 (40)		2 (66.7)			1 (50)		1 (50)	1 (50)	
Median hospitalization	47 (3-127)	14 (5-99)	21 (8-35)	18.5 (13-43)	28 (26-89)	20 (1-64)	20 (19-35)	16 (11-21)	26.5 (20-33)	23.5 (4-43)	19.5 (7-32)	15 (10-50)

*Not all data available

We deplored 43 or (30.5%) cases of death in our study population and 20 cases or 14.2% of sequelae. The median length of hospital stay was 18 (0-874).

4. Discussion

The implementation of such an algorithm requires having robust elements on the infectious causes of the cases observed in the studied region, in order to prioritize and rationalize the diagnostic tests to be conducted. This rationalization will allow optimized diagnostic and therapeutic implementation. At the same time, this precise description of the causes could lead to the implementation of specific health actions targeting certain vaccine-preventable infections, for example. For this, it was important to collect a lot of data in order to ultimately have as exhaustive an analysis as possible of the demographic, clinical, biological, diagnostic and therapeutic data of the included cases. Thus, our study presents strong points, making it possible to meet the proposed objectives. Furthermore, it was important that this study be based on the structures in place, the additional analyzes carried out in the Lyon laboratory ultimately only allowing better microbiological documentation of the cases observed in Batna. To our knowledge, this is the first prospective study of this size carried out in Algeria and Africa, and whose size is comparable to those carried out for the same objectives in the United States, the United Kingdom or France. The incidence observed during our work is 9.58 encephalitis/100,000 hospitalizations, a fairly high rate compared to Italian (5.88/100,000 hospitalizations) or Australian (5.2/100,000 hospitalizations) data (14, 15). Overall, publications on encephalitis case cohorts show that these are rather rare infections, with an annual incidence estimated between 3.5 and 7.4 per 100,000 inhabitants (1, 16, 17), with some differences across studies. Several studies suggest a lower incidence, whether in the United States (1, 18-22), Sweden (23), the United Kingdom or France (24).

In our study, on the basis of the population pool drained by the hospital structure which participated in this work, we can estimate that the overall annual incidence of encephalitis and meningoencephalitis was 2.15 / 100,000 inhabitants, with a variation depending on years (1.7/100,000 inhabitants in 2012, 3.38/100,000 inhabitants in 2013, 2.03/100,000 inhabitants in 2014 and 1.52/100,000 inhabitants in 2015). This variability in incidence could be explained by the pronounced seasonality of some pathogens (Adenovirus, Coronavirus, Rhinovirus), or due to the emergence/re-emergence of certain other germs (West Nile) (25, 26). Such variability has already been reported in a study carried out over a period of 10 years at the level of National Health Service hospitals in England and Wales, showing an incidence varying between 0.6/100,000 (in 2004) and 3.9/100,000 inhabitants (in 2013) (27).

The average age of our population is 30.8 years, with a median of 28 years and extremes of 90 days and 83 years. This average age is similar to those reported in two British studies (28,27), or a French study where the average age was 38 years (24). On the other hand, during a study carried out in Thailand between July 2003-August 2005, the median age was 12 years. This difference may be linked to the frequency of cases of Japanese encephalitis which quite frequently affects Asian children, and which is not found in Europe or Africa (29).

On the etiological level, the comparison with certain studies already published is interesting (California 98-2005 (30) England 2005-2006 (28), France 2007 (11), Thailand 2003-2005 (29), PMC 2000-2002 (24 In Batna, a wide range of pathogens cause acute encephalitis. In this study, using a comprehensive approach and state-of-the-art diagnostic methods, the etiology was identified for 111 cases (78.7%) versus 52% in France (11), 63% in England (28), 10.8% in California (19, 30), 19.9% in PMSI France (24), 65.8% in Thailand (29). In the light of our study, the monomicrobial etiology was identified for 63 patients (44.7%), co-infections were identified for 48 patients (34%), of which 12 (8.5%) had more than 2 identified pathogens. Among the etiologies confirmed for 58 patients (41.2%) compares to 77% in France (11), 33% in England (28), (24.8%) in Thailand (31). The diagnosis was probable for 41 patients (29.1%) against 14% in France (11), 9.4% in England (28), 17 (11.4%) in Thailand (31). The diagnosis of a possible etiology was detected for 12 patients (8.5%) against 12 (9%) in France 2007 (11). There were 32 possible etiologies (18.3%) against 3 (2%) in France (11), 44 (29.5%) in Thailand (31). Among the 111 cases identified; patients with a confirmed and or probable etiology were 55 viruses (59.6%) and 39 bacteria (35.2%) against 90 viruses (59%) and 40 bacteria (26.3%) in France (11). In our study and taking coinfections into account, the most frequently identified etiological pathogen was tuberculosis 30 (21.3%), which is endemic in Algeria, followed by EBV 20 (14.2%), HSV 14 (9.9%).) and CMV 11 (7.8%). Compared to the study carried out in France (11), the respective frequencies were 15.2% for tuberculosis, 42% for HSV, 15.2% for VZV and 10% for Listeria. In England (485); the three most frequent etiologies were tuberculosis (5%), VZV 10 (%), and streptococcus (2%) and finally, the study carried out in California (30), reported 25% enterovirus and 24% HSV. These results are ultimately quite heterogeneous, with some particularities, in particular the involvement of the coronavirus, reinforced by the study carried out in China in 2018 (32, 33), 1 case of influenza B (Yamagata) of which no case was the subject from one publication, 2 cases of HRV C44 rhinovirus, one probable sporadic Creutzfeldt Jacob case, a high proportion of adenovirus 6 (4.2%) compared to other studies (34, 35). 1 West Nile case, against 621/1071 cases collected in Tunisia during the period 2003-2009(36), 6 possible Rickettsia cases vs 3 cases in Thailand (37), including

3 R.Typhi, 2 R.Conorrii, 1 R. Rickettsia (meningoencephalomyelitis with skin involvement and haematuria). None of the samples were positive for Henselae Bartonella or Trophyeryma whipplei, or Toscana, or Measles, or Parechovirus. For all documented infections apart from co-infections, the search for patients with a monomicrobial agent was 63 (44.7%) (see Table No. 4), whose confirmed and/or probable etiology was at number of 53 (37.6%) were essential to come out with a decision algorithm as to the diagnostic approach. For these patients, the onset was gradual in (52.8%). Meningeal involvement was evident for the majority of infectious agents (77.4%). LP was lymphocytic in 54.7% of cases, polymorphonuclear in 28.3%, and variegated in 7.5%. The management of acute meningoencephalitis is a real challenge given the multiplicity of causes and the frequency of atypical forms. It is rare for the etiological diagnosis to be obvious on admission. Despite the high proportion of patients for whom large volumes of CSF and serum were collected for testing with a wide range of routine and sophisticated diagnostic tests, the etiology of a quarter of patients remained unknown. Likewise, nearly a third of the diagnoses proposed are only possible diagnoses, with a level of evidence too low to be certain of the result. However, the proportion of cases for which the etiology remains unknown or uncertain is lower than those reported in French (13), British (38), or American (39) studies. This difference can be explained by the very large number of diagnostic tests performed (up to 31) often done simultaneously rather than sequentially. This diagnostic richness provides valuable information for the creation of a decision-making algorithm. However, the one we wish to propose is essentially based on proven monomicrobial infections.

Furthermore, this study highlights the diagnostic difficulty observed when a cocktail of pathogens is detected. The power of diagnostic tools sometimes poses a problem, especially for pathogens responsible for persistent infection and whose frequency is high. Thus, the role of EBV, an agent known to cause encephalitis, and which occupies the second place in the frequency of etiologies in our study, remains to be elucidated. The high incidence of EBV infections in Algeria as evidenced by the high number of nasopharyngeal cancers linked to EBV makes it perfectly possible that it is a major player in encephalitis in Algeria. The efforts needed to improve diagnosis and reduce mortality rely on the use of appropriate decision-making algorithms for adults and children with encephalitis, defining a priori a standardized approach using on-site diagnostic tools, adapted to the context. Such an approach will facilitate research and collaboration around the world and enable clinicians to provide appropriate clinical care for patients with this serious and sometimes fatal neurological syndrome. A similar multicenter study would have been interesting in the South, center, and West of the country in order to compare the etiologies. Microbiological analysis of CSF, by PCR, remains the main step and the cornerstone of diagnosis, supplemented by brain imaging, less specific but increasingly efficient. The development and dissemination of diagnostic techniques, mainly viral PCR, should allow both a reduction in the proportion of meningoencephalitis of unidentified etiology, and a significant improvement in the prognosis through the rapid establishment of a specific treatment initiated early, particularly in cases of herpetic, listerial and tuberculous meningoencephalitis. Through the results of our study, we therefore propose the following algorithms for the management of encephalitis (figures 1 to 3).

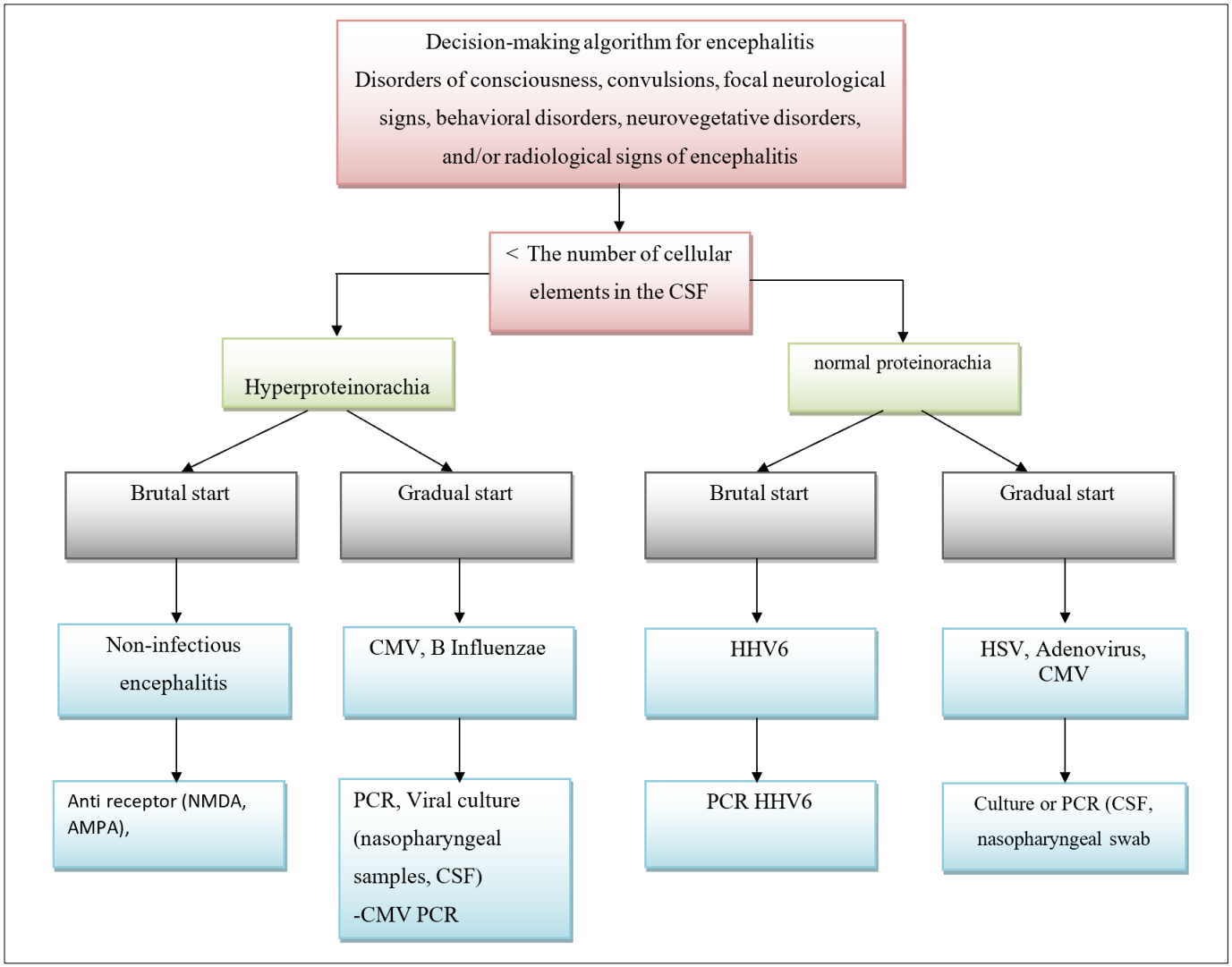

Figure 1 Decision-making algorithm for encephalitis. Disorders of consciousness, convulsions, focal neurological signs, behavioral disorders, neurovegetative disorders, and/or radiological signs of encephalitis

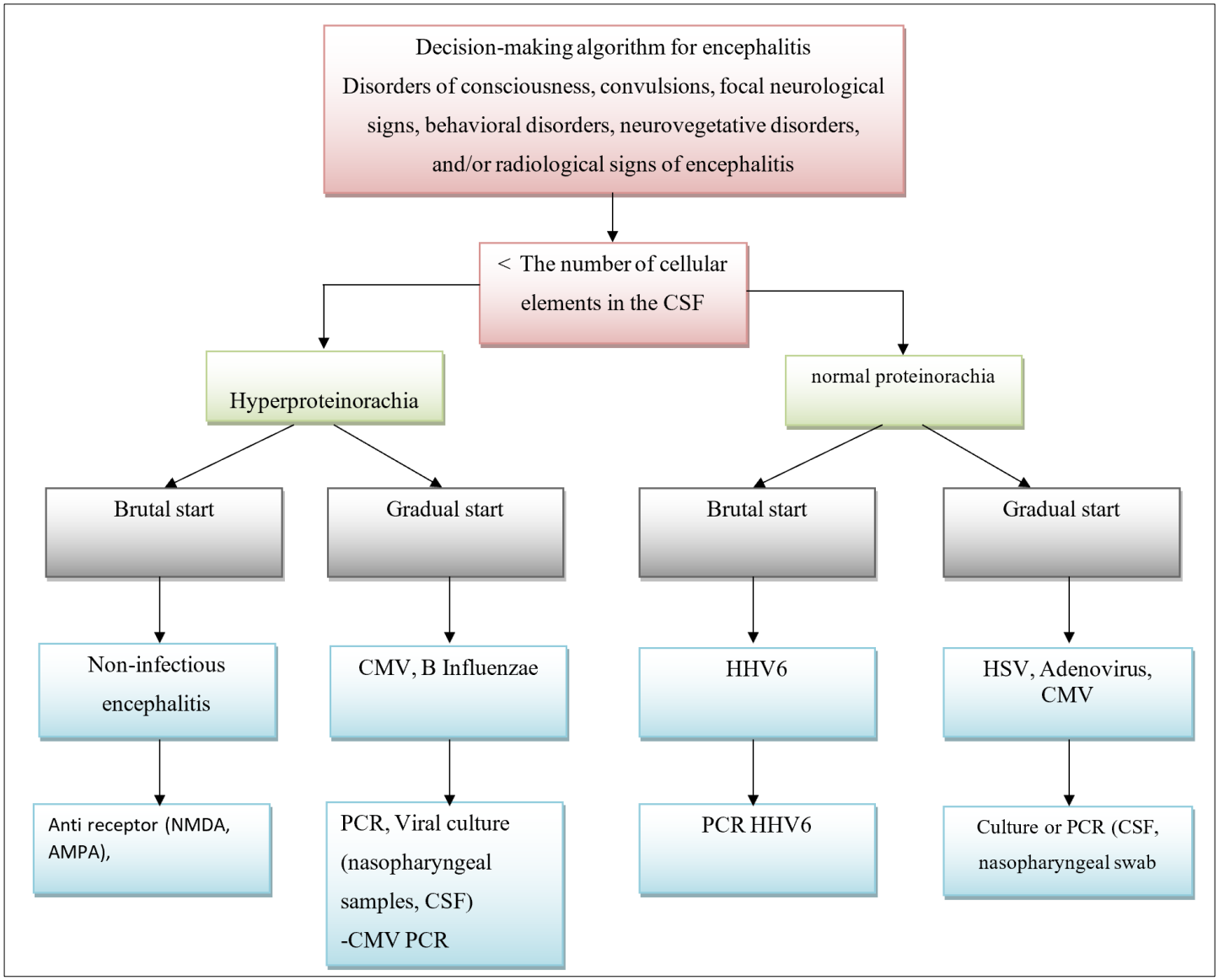

Figure 2 Decision-making algorithm facing of meningoencephalitis. Disturbances of consciousness, convulsions, focal neurological signs, behavioral disturbances, neurovegetative disorders, and/or radiological signs of febrile encephalitis with disturbed CSF

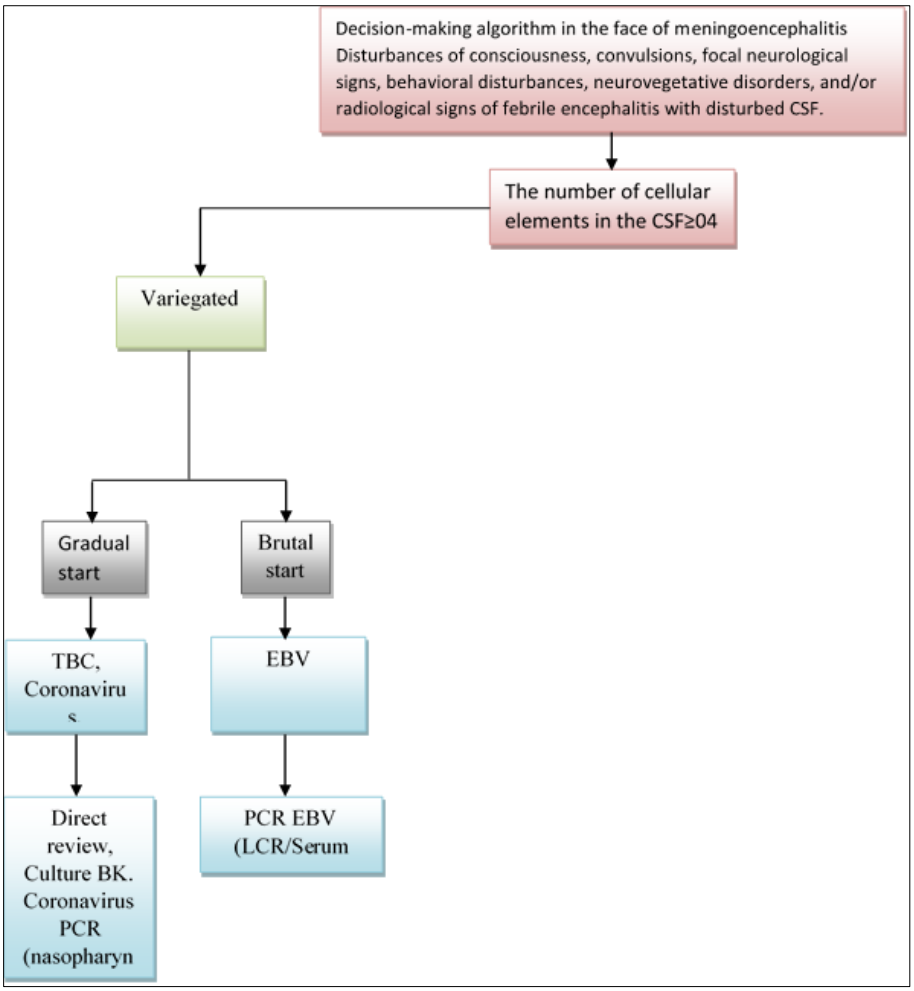

Figure 3 Decision-making algorithm in the face of meningoencephalitis. Disturbances of consciousness, convulsions, focal neurological signs, behavioral disturbances, neurovegetative disorders, and/or radiological signs of febrile encephalitis with disturbed CSF

Advances in PCR, syndromic approaches currently proposed (FilmArray) allowing the performance of multiplex PCR tests are promising tools that remain to be evaluated. Similarly, innovative amplification techniques coupled with high-throughput sequencing (also called NGS for Next Generation Sequencing) may make it possible to identify new pathogenic agents responsible for some of the encephalitis of as yet unknown etiology, or to be even more sensitive than PCR. As a preamble to our research work, and in addition to the proposed algorithms, we thus wished to propose a non-exhaustive minimum list of infectious agents which seemed necessary to us to search for during encephalitis. These pathogens are classified by level (1, 2, 3 and HC) according to the frequency of positivity observed during our study. However, this proposal must in no way constitute an obstacle to the proper care of patients, for example by extending the time required to obtain results likely to modify the treatment. All of us must keep in mind that the urgency in encephalitis is therapeutic management, more than diagnostic management. The latter must be at the service of therapeutic management.

Encephalitis remains a real problem of etiological diagnosis and medium- and long-term management. Infectious recovery does not necessarily indicate complete recovery and it is appropriate to focus on a systematic neuropsychological assessment at the end of the acute episode to identify possible after-effects. The future lies in the research and development of new antiviral treatments, particularly for emerging viruses. The objective of the investigations of these studies was to fuel the discussion around the improvement in the management of encephalitis in Algeria, and to emphasize three points for improvement:

- Perfect surveillance systems in a “one-health” perspective with existing means and systems;
- Regularly conduct epidemiological surveys to develop diagnostic strategies to better identify infectious agents (viruses or bacteria) quickly and reliably.

- To encourage collaborations on the national and international level.

Internet technology makes it possible to record new diseases and quickly disseminate information on their characteristics and geographic distribution. We need to remember that infectious diseases know no borders.

5. Conclusion

Despite intensive efforts to diagnose cases, this study also highlights the need for improved diagnostic strategies and appropriate clinical testing algorithms for adults and children with encephalitis with modification of the priority of the etiology investigated by level based on the results obtained during our work in order to provide a standardized approach for the evaluation of patients suspected of encephalitis, and the implementation of on-site diagnostic tools (real-time PCR, Serology) and the improvement of management in intensive care must certainly have an effect on mortality.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Batna. Before enrollment, all patients received information on the aims and procedures of the study, and were included only after they expressed their willingness to participate.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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